IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jo Klaveness et al.
Application No.	:	10/573,606
Filing Date	:	March 28, 2006
Art Unit	:	6864
Title	:	Optical Imaging of Colorectal Cancer
Docket No.	:	PN0368

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Commissioner for Patents
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APPEAL BRIEF

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I. REAL PARTY IN INTEREST

The real party in interest in this Appeal is GE Healthcare, Inc., a part of General Electric "GE".

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to the instant appeal.

III. STATUS OF CLAIMS

Claims 13, 15-18, and 20-24 are pending in this application. The Examiner has rejected all of these claims. Claims 13, 15-18, and 20-24 as amended during prosecution are reproduced in the **Claims Appendix** attached hereto. Appellants are appealing the rejections of Claims 13, 15-18, and 20-24.

IV. STATUS OF AMENDMENTS

Appellants filed a Response on September 12, 2007 and a final Office Action was mailed on September 24, 2007. No claims were amended subsequent to the Examiner's final rejection that was mailed on September 24, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1 describes an optical imaging contrast agent with affinity for an abnormally expressed biological target associated with colorectal cancer (CRC). The contrast agent is of formula I:

V-L-R (I)

wherein:

V is one or more vector moieties having affinity for an abnormally expressed target in CRC, where said target is selected from c-met, MMP-14, COX-2, beta-catenin and cathepsin B;

L is a linker moiety or a bond, and

R is one or more reporter moieties detectable in optical imaging, wherein the contrast agent has a molecular weight below 10,000 Daltons.

Support for claim 1 can be found on page 7, lines 10-30 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from a Final Rejection that was mailed on September 24, 2007. The Examiner rejects claims 13, 15-18, and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Marten *et al.* (Gastroenterol., 122, 406-414 (2002) ("Marten") in view of Klaveness *et al.* U.S. Patent No. 6,610,269B1) ("Klaveness") and in further view of Waggoner et al. U.S. Patent No. 6,008,373 ("Waggoner").

The Examiner also rejects claims 13, 15-18,and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Weissleder *et al.* (Nature Biotech., 1999, 17, 375-378) ("Weissleder") in view of Klaveness and further in view of Waggoner.

Claims 15-18 and 20-24 are dependent on claim 13 and inherit all the limitations set forth in claim 13. Therefore, the issues in this appeal are:

1. Whether Marten or Weissleder in view of Klaveness and further in view of Waggoner disclose, teach, or suggest all the elements of claims 13, 15-18, and 20-24?

VII. ARGUMENT

The Examiner rejects claims 13, 15-18, and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Marten *et al*. (Gastroenterol., 122, 406-414 (2002) ("Marten") in view of Klaveness et al. U.S. Patent No. 6,610,269 B1) ("Klaveness") and in further view of Waggoner et al. U.S. Patent No. 6,008,373 ("Waggoner").

The Examiner also rejects claims 13, 15-18,and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Weissleder et al. (Nature Biotech., 199, 17, 375-378) ("Weissleder") in view of Klaveness and further in view of Waggoner.

Appellants respectfully request that The Board of Patent Appeals and Interferences ("Board") should reverse the Examiner's rejections for the reasons set forth below.

A. The Examiner's Rejections of Claims 13, 15-18, and 20-24 Should be Reversed Since Marten or Weissleder in view of Klaveness and further in view of Waggoner Fail to Teach All the Elements of the Claims

Before discussing the specific differences between the prior art and the present invention, Appellants respectfully submit that it is impermissible within the framework of 35 U.S.C. §103 to pick and choose from any one reference only so much of it as will support a

given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). (emphasis added).

On pages 2 and 3 of the final Office Action dated September 24, 2007 ("Office Action"), the Examiner suggests that it would have been obvious for the person skilled in the art to utilize the cathepsin B sensing NIR fluorochrome probes of Marten for imaging the colon. Appellants point out that the cathepsin B sensing probe of Marten is described on page 408 of Marten in the text subtitled "NIR Fluorochrome Probes". The statement is made that:

"The assembly consisted of a synthetic graft copolymer containing partially pegylated (5 kDa) poly-*L*-lysine (35 kDa)....."

Marten states (same location):

"The NIRF probe contained Cy5.5 monofunctional dye (Amersham Pharmacia Biotech, UK) reporters adjacent to ..K-K...cleavage sites on a macromolecular assembly, described in more detail elsewhere.[20] "

Reference 20 of Marten is the reference Weissleder. The experimental section of Weissleder states that the graft copolymer had an average molecular mass of 480 kDa – see the section subtitled "experimental protocol" (p.377, first two sentences). The probes of Marten and Weissleder are thus the same and far exceed the molecular weight limit of 10,000 Daltons (10 kDa) of present claim 13.

Use of the probes described by Marten in the manner suggested by the Examiner therefore falls outside the scope of Claim 13. Similar logic applies to claims 15-18 and 20-24 since these claims depend on, or refer to claim 13.

Marten neither discloses, teaches, or suggests a contrast agent of its disclosure of having a molecular weight of below 10,000 Daltons. In fact, the probe used in Marten clearly falls outside the scope of present claim 13.

Therefore, the claims of the present invention cannot be merely assumed obvious from the Examiner's subjective view point. Appellants note that "the prior art itself must provide a motivation or reason for the worker in the art, without the benefit of the Applicant's specification, to make necessary changes in the reference device". See, *Ex parte Chicago Rawhide Manufacturing Co.*, 226 U.S.P.Q. 438 (PTO Bd. App. 1984).

The Examiner suggests (Paragraph 7) that it would have been obvious to minimize the molecular weight of the fluorochrome probes of Marten "by minimizing the linker molecular weight or the number of detectable reporter moieties to provide probes having greater penetration into cellular environments."

The fluorochrome probe of Marten is the same as that of Weissleder (*see above*). Appellants contend that the modification suggested by the Examiner is in direct contradiction to the teaching of Marten/Weissleder, and is thus an invalid construction. Thus, Weissleder (p. 375 left hand column) teaches:

"Tumoral delivery of the quenched NIRF probes is facilitated by a novel, long, circulating, synthetic graft copolymer that has been recently tested in clinical trials. The copolymer accumulates in tumors by slow leakage across highly permeable neovasculature…

We describe the construction and testing of a model quenched copolymer and demonstrate that it is possible to detect micrometer-sized tumors *in vivo* using this strategy."

The copolymer of Marten/Weissleder is thus described by the references themselves as an essential feature, contributing to the strategy and mechanism of tumor uptake. That being the case, modification of any linker group and/or number of conjugated reporter molecules of the probes of Marten/Weissleder, as suggested by the Examiner would not change the fact that a copolymer of average molecular weight 480 kDa is always involved. The modifications of the linker group and/or reporter suggested by the Examiner would therefore inevitably lead to probes outside the scope of the present claims, because the vector (i.e. the graft copolymer) remains a 480 kDa species.

Appellants further point out that the person skilled in the art could have no motivation to drastically reduce the molecular weight of the probes of Marten/Weissleder, since those references teach that the high molecular copolymer is an essential part of a successful strategy for tumor imaging.

Klaveness is assigned to Appellants, GE Healthcare, Inc., and specifically relates to a composition of matter for claimed formula (I) V-L-R;

where V is a vector for angiogenesis;

R is a detector; and

L is an optional linker group.

The Examiner refers to the teaching of Klaveness on the molecular weight of the linker (Column 36 lines 57-64). Applicants firstly point out that the contrast agents of Klaveness are of formula V-L-R, where the linker (L) is optional ("L is a linker group or a bond" – Claim 1 of Klaveness). Firstly, applicants contend that the person skilled in the art could have no motivation to modify a second reference based a feature taught by a first reference to be merely optional. Secondly, whilst Klaveness does indeed comment on the molecular weight of the linker, Klaveness is silent on the overall molecular weight of the contrast agent (i.e. V-L-R). Thus, Klaveness does not expressly teach or suggest that the contrast agent should have a molecular weight below 10,000 Daltons. Klaveness (Column 36 line 58) teaches that the linker can have a molecular weight up to 2MDa, generally 100 to 100,000 Da especially 120 to 20,000 Da (Column 6, lines 62-64). Hence, Klaveness merely teaches a wide range of molecular weights for the linker. The Examiner's alleged motivation for reducing the molecular weight of the contrast agent based on Klaveness is thus absent and believed to be invalid, since it is based on an incorrect analysis of the teaching of Klaveness.

In view of Klaveness, Appellants respectfully point out here that it is well settled in the law that a reference must be considered not just for what it expressly teaches, but also for

what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994).

Waggoner (US 6,008,373) discloses a low molecular weight fluorescent labeling complex. Appellants point out that the 'complex' of Waggoner refers to a first and second fluorochrome, not a conjugate with a protein (see Waggoner Column 2 lines 38-44). The proteins of Waggoner are defined within the term 'target material' (see Claim 1 of Waggoner plus Column 3 lines 5-29). Thus, the "complexes" of Waggoner have a functional group ("target bonding group") to permit attachment to a target material or target compound (Waggoner Column 3 lines 5-20), which is something additional to the 'complex'. The Examiner refers to Waggoner Column 6 lines 15-22, where it is stated:

> "The fluorescent labeling complexes of the invention have low molecular weights and can be readily conjugated to antibodies, other proteins, and DNA probes. Low molecular weight as used herein shall mean that the combined molecular weight of the fluorochromes and linker of the complex is between about 500 and 10,000 Daltons, and for a two fluorochrome complex, preferably in the range of 1000 to 2500 Daltons. Therefore, these labeled species will have much greater penetration into intracellular environments than is possible with the large phycobiliprotein labels currently in use." [emphasis added].

Thus, the teaching of Waggoner on molecular weight refers only to the complexes, not the species to which a targeting molecule has been conjugated. That is believed clear from

the section of text cited, plus Claim 8 of Waggoner which is silent on the 'target material' and refers only to the first and second fluorochromes and the linker.

Appellants point out that Waggoner teaches (Column 3 lines 21-25):

> "The target may be antibody, antigen, protein, enzyme, nucleotide derivatized to contain one of an amino, hydroxyl, sulfhydryl, carboxyl or carbonyl groups, and oxy or deoxy polynucleic acids derivatized to contain one of an amino, hydroxy, sulfhydryl, carboxyl or carbonyl groups, cells, polymer particles or glass beads."

Waggoner does not teach the molecular weight of the "target", hence Waggoner is silent on the molecular weight of the species:

[fluorescent labeling complex]-[linker]-[target material.

Hence, as with Klaveness, Appellants contend that the alleged motivation towards contrast agents of molecular weight less than 10,000 Da based on Waggoner is invalid, since it is based on a misconstruction of the teaching of the reference. Furthermore, Waggoner is not even of the same utility as the present invention, since it is silent on both *in vivo* imaging and contrast agents. Unlike the current invention, Waggoner does not disclose, teach, or suggest an optical imaging contrast agent that has affinity for an abnormally expressed biological target associated with colorectal cancer. Further, unlike the present invention, Waggoner does not disclose, suggest, or teach formula (I) let alone disclose how a vector, linker, and reporter are combined to provide a contrast agent suitable for *in vivo* imaging having a molecular weight of below 10,000 Daltons.

Appellants therefore respectfully request that the Board should reverse the Examiner's obviousness rejection of claims 13, 15-18, and 20-24.

CONCLUSION

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 13, 15-18, and 20-24 as set forth in the Office Action mailed September 24, 2007, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: February 19, 2008

Respectfully submitted,

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VIII. CLAIMS APPENDIX

Claim 1-12 (Cancelled)

13. (Previously presented) An optical imaging contrast agent with affinity for an abnormally expressed biological target associated with colorectal cancer (CRC), said contrast agent being of formula I:

V-L-R (I)

wherein:

V is one or more vector moieties having affinity for an abnormally expressed target in CRC, where said target is selected from c-met, MMP-14, COX-2, beta-catenin and cathepsin B;

L is a linker moiety or a bond, and

R is one or more reporter moieties detectable in optical imaging,

wherein the contrast agent has a molecular weight below 10,000 Daltons.

14. (Cancelled)

15. (Previously presented) A contrast agent as claimed in claim 13 wherein R is a cyanine dye.

16. (Previously presented) A contrast agent as claimed in claim 13 wherein the target is a receptor or a non-catalytical target.

17. (Previously presented) A contrast agent as claimed in claim 13 comprising a contrast agent substrate, wherein the target is an abnormally expressed enzyme, such that the contrast agent changes pharmacodynamic properties and/or pharmacokinetic properties upon a chemical modification from a contrast agent substrate to a contrast agent product upon a specific enzymatic transformation.

18. (Previously presented) A contrast agent as claimed in claim 17 wherein the contrast agent changes binding properties to specific tissue, membrane penetration properties, protein binding or solubility properties upon the chemical modification.

19. (Cancelled)

20. (Previously presented) A contrast agent as claimed in claim 13 wherein V is selected from peptides, peptoid moieties, oligonucleotides, oligosaccharides, lipid-related compounds and traditional organic drug-like small molecules.

21. (Previously presented) A contrast agent as claimed in claim 20 wherein V is a peptide.

22. (Previously presented) A pharmaceutical composition for optical imaging for diagnosis of CRC, for follow up of progress of CRC development or for follow up of treatment of CRC, comprising a contrast agent as defined in claim 13 together with at least one pharmaceutically acceptable carrier or excipient.

23. (Previously presented) A contrast agent as claimed in claim 13 for the manufacture of a diagnostic agent for use in a method of optical imaging of CRC involving administration of said diagnostic agent to an animate subject and generation of an image of at least part of said subject.

24. (Previously presented) A method of generating an optical image of an animate subject involving administering a contrast agent to the subject and generating an optical image of at least a part of the subject to which the contrast agent has distributed, characterized in that a contrast agent as defined in claim 13 is used.

IX. EVIDENCE APPENDIX

Appellants hereby list the following journal articles/patents that the Examiner cites against the present invention. Appellants enclose the below referenced journal articles herein.

Marten *et al.* (Gastroenterol., 122, 406-414 (2002):

U.S. Patent No. 6,610,269B1) ("Klaveness")

U.S. Patent No. 6,008,373 ("Waggoner")

Weissleder *et al.* (Nature Biotech., 199, 17, 375-378)

This is the evidence relied upon by the Examiner for rejection of appealed Claims 13, 15-18, and 20-24 in the Office Action dated September 24, 2007.

X. RELATED PROCEEDINGS APPENDIX

There are no other appeals or interferences related to the instant appeal.